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Allometric Respiration/Body Mass Data for Animals to be Used for Estimates of Inhalation Toxicity to Young Adult Humans

R. W. Bide,* S. J. Armour and E. Yee
Defence Research Establishment Suffield, Box 4000, Medicine Hat, Alberta, Canada, T1A 8K6

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The relationship between body weight (*BW*) and respiratory minute volume (V_m) was reviewed by collecting a database from the literature. The data were separated into anaesthetized and non-anaesthetized groups. Only young adult terrestrial mammals were included in the final data set. This database is the largest to be reported to date, is the first to separate the anaesthetized and non-anaesthetized groups and is matched to the target population of young, fit adult humans. The data set of non-anaesthetized animals contained 142 studies representing 2616 animals and 18 species from mice at 12 g body weight to horses and a giraffe at ca. 500 kg body weight. Analysis of the data indicated a power law (allometric) relationship between the minute volume and body weight. The resulting allometric equations for the empirical relationship between minute volume and body weight are: $\log_{10} V_m = -0.302 + 0.809 \log_{10} BW$ and $V_m = 0.499\, BW^{0.809}$, where V_m is the minute volume (l min^{-1}) and *BW* is the body weight (kg). From these equations, a minute volume of 15.5 l min^{-1} was obtained for a 70 kg human in the same physiological and/or emotional state as the animals. The results of the analyses were compared to other empirical studies in the literature, the more recent of which also indicated a scaling factor of 0.8. The relationship between minute volume and body weight is recommended for use in estimating the inhalation toxicity to young adult humans (military personnel), because this is the first study to use a large database focused exclusively upon non-anaesthetized young adult terrestrial mammals. **Copyright © 2000 Crown in the right of Canada. Published by John Wiley & Sons, Ltd.**

INTRODUCTION

The assessment of human hazards from chemical exposures, whether deliberate or accidental, requires a knowledge of allometry: the study of the differential relationships of metabolism, physiology and respiration between species. In this case, the comparison is between man and other mammalian species, particularly those species commonly used for laboratory and agricultural experimentation. The requirement is particularly important when inhalation exposures are to be assessed because the doses received are not defined directly (as in direct injection/feeding routes of chemical introduction) but rather inferred from atmospheric and respiration parameters. With most hazard assessments, there is little information concerning direct human exposures and the toxicity estimates must be made by extrapolating animal data to assess the human condition.

Comparative physiologists and, more recently, toxicologists have provided a wealth of information concerning the relative respiration rates, tidal volumes and other respiratory parameters. Several comparative studies have been published[1–8] relating the body weight, body surface and alveolar surface areas to these parameters in mammals. As technology has improved, the methods of measuring these functions have progressed[9] from procedures requiring anaesthesia and surgical intervention[10] to direct measurements on intact animals in enclosed chambers.[6,11–18] In the process, the effects of using no anesthetic[19,20] and using single and combinations of anaesthetics[21–23] have been studied. In retrospect, it is clear that the animal data concerning respiratory function must be grouped such that the emotional/physiological state of the animals is as similar as possible and the comparative human values must be matched to similar animal data.

In inhalation toxicology, the dose received by an animal is directly related to the amount of air inhaled.[3,24,25] The important inter-related respiratory measurements are the respiration rate, the tidal volume and the minute volume. Several authors have attempted to relate minute volumes to the body weight of animal species.[1–5,24] Although the process is generally agreed, the data and resulting mathematical values are quite different (Table 1). Although some convergence may be noted in the most recent compilations, these data sets have been promulgated by authors from the same institutes. Upon investigation, it was apparent that the data in three cases[2,4,8] were derived from a mixture of anaesthetized and non-anaesthetized animals, and another[3] could not be traced readily to published data. For this report, a relatively large number of studies providing body

* Correspondence to R. W. Bide, Defence Research Establishment Suffield, Box 4000, Alberta, Canada, T1A 8K6. E-mail: rbide@dres.dnd.ca

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Table 1. Comparison of minute volume/body weight data from various literature sources

	Minute volume/body weight ratio (l min^{-1} kg^{-1})					
Species	Crossfill & Widdicomb[1] (Anaesthetic)	Guyton[2] (Anaesthetic)	Guyton[2] (No anaesthetic)	Snipes[3] (No anaesthetic)	USEPA[4,a] (Mixture of anaesthetic)	This report (No anaesthetic)
Mouse	0.66	1.15	1.239	1.3	1.152	1.491
Hamster	–	0.500	0.665	–	0.731	0.474
Rat	0.64	0.668	0.638	0 80	0 615	0 833
Guinea pig	0 19	0.323	0.334	0.66	0.475	0.596
Rabbit	0.26	0.387	–	–	0.332	0.413
Cat	0.26	–	–	–	0.335	0.257
Dog	0.25	–	–	0.36	0.258	0.356
Monkey	0 29	–	0.322	0.29	0 257	0 374
Baboon	–	–	–	–	–	0.365
Goat	–	–	–	–	0.235	0.263
Sheep	–	–	–	–	0.298	0.289
Pig	–	–	–	–	0 241	0.138
Donkey	–	–	–	–	0.159	0 163
Pony	–	–	–	–	0.208	0 183
Mule	–	–	–	–	0 093	0 123
Horse	–	–	–	–	0 118	0.133
Cow	–	–	–	–	0 253	0.208
Man (70 kg unless noted)						
Quoted	0.0914	0.127[b]	0 128	0.09	0.286	–
Calculated[c]	0.146	0.142	0.127	0 18	0 164	0 222
Breathing rates for man (l min^{-1})						
Quoted	6 4	8.7[c]	8 7	20	20[d]	–
Calculated[c]	10 2	10.0	8 9	12.4	10 6	15.5

[a] USEPA values were derived either from the allometric equations given for combined species or as the average value of the appropriate data presented for that species.
[b] Value for 68 5 kg man.
[c] Values calculated from the matching allometric equations.
[d] Another USEPA document[34] lists 13 8 l min^{-1}.

weight/respiratory volume data have been collected, reviewed, tabulated and the data compared to previous attempts to relate body weight and minute volume. Relationships between body weight and minute volume have been derived for anaesthetized and non-anaesthetized animals and formulae provided to assist in the assessment of hazard to young adult humans from mammal toxicity data.

EXPERIMENTAL

The data gleaned from the literature for physiological condition, body weights, minute volumes and the numbers of animals used were tabulated and mean values for each species and the standard deviation of the data were calculated using FRAMEWORK IV (originally Ashton-Tate Corp., Torrance, CA; now Selections & Functions, Inc., Scituate, MA 02066). When the number of data in a group (N value) was <4, standard deviations were not reported. The data were divided into anaesthetized and non-anaesthetized groups. The values for body weight and minute volume were plotted for all the data in each group and for each species in each group, and the results were evaluated. A linear regression was calculated for each major group using a log–log relationship between the minute volume and body weight.

The data analysis was conducted using S-PLUS Version 3.4 for UNIX (Mathsoft, Inc., Seattle, WA) running on a Hewlett-Packard model 715/50 workstation under HP-UX (Hewlett-Packard, 3000 Hanover St., Palo Alto, CA). The S-PLUS provides an interactive and integrated computing environment consisting of a suite of software facilities for programming, graphics and statistical analysis. All the computations were performed in double precision (64-bit precision of a 32-bit computer). The computed numbers are carried and calculated with 14 decimal places.

RESULTS

Evaluation of data collected from the literature

The full data collection encompasses 117 papers covering 24 species and tabulating 243 experimental groups and data from 3455 animals ranging in size from mice at 0.012 kg to horses and a giraffe at 480–550 kg. The data, summarized in Tables 2 and 3, were divided

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Table 2. Average body weights (*BW*), minute volumes (*MV*) and *MV/BW* ratios for non-anaesthetized animals

Species	Body weight[a] (kg)	Minute volume (l)	$\frac{MV}{BW}$	Species	Body weight (kg)	Minute volume (l)	$\frac{MV}{BW}$
Cat	$3.36^{32,5}$ ±0.480	0.845 ±0 061	0.257 ±0.052	Pony	$167^{3,3}$ ±35	29 4 ±13.8	0.183 ±0.092
Cows	$323^{46,20}$ ±98	66 ±28	0 208 ±0 067	Horse	$465^{27,4}$ ±29	62 ±14	0.133 ±0.029
Donkey	$120^{1,1}$	19 5	0 16	Mule	$210^{2,2}$	25 9	0.12
Dog	$13\ 0^{739,21}$ ±10.7	4 23 ±1 94	0.356 ±0.093	Sheep	$52.6^{48,11}$ ±15.2	13 9 ±7 2	0.289 ±0.160
Guinea pig	$0.323^{532,19}$ ±0 109	0.182 ±0.041	0.596 ±0.140	Pig	$197^{2,2}$ ±39	26 ±13	0 138 ±0 037
Goat	$36.9^{36,4}$ ±12.3	9.6 ±2 8	0.263 ±0.052	Giraffe	$544.^{2,1}$	74	0.136
Hamster	$0.111^{97,4}$ ±0.016	0.051 ±0.008	0.474 ±0.142	Rabbit	$2\ 77^{61,3}$ ±0.63	1.453 ±0.193	0.413 ±0.787
Mouse	$0\ 0207^{74,4}$ ±0.0065	0.031 ±0.014	1 491 ±0.366	Rat	$0.261^{284,21}$ ±0.069	0.203 ±0.079	0.833 ±0.434
Cotton rat[b]	$0.077^{27,1}$	0.040	0.516	Baboon	$4.42^{4,1}$	1.61	0.365
Spiny anteater[b]	$3.47^{3,2}$ ±0.177	0 527 ±0.251	0 150 ±0.065	Monkey	$4.27^{311,15}$ ±2 82	1.40 ±0.49	0.374 ±0.131

[a] Superscript values on the body weight data are number of animals and number of studies, respectively.
[b] Excluded from analysis (see text).

into non-anaesthetized (Tables 2, 4) and anaesthetized (Tables 3, 5) groups and treated separately. Although data for birds were available and have been used in other summaries,[4] they were not included here because of the marked physiological and morphological differences[26,27] between birds and mammals. Data for man were also excluded because one aim of the study was to obtain a theoretical value for man and because there was no simple method of equating the physiological and emotional states of the test animals and humans, i.e. which of the many human values available were to be used. Studies with humans[3,28–30] commonly involve

Table 3. Average body weights (*BW*), minute volumes (*MV*) and *MV/BW* ratios for anaesthetized animals

Species	Body weight[a] (kg)	Minute volume (l)	$\frac{MV}{BW}$	Species	Body weight (kg)	Minute volume (l)	$\frac{MV}{BW}$
Cat	$3.08^{101,13}$ ±0.381	0.680 ±0.277	0.217 ±0.070	Giraffe	$544.^{1,1}$	61	0.111
Dog	$11.65^{135,11}$ ±4 02	2.63 ±1.44	0.234 ±0.112	Rabbit	$2.89^{74,6}$ ±1.12	0.667 ±0.141	0 250 ±0.086
Ferret	$0.314^{18,1}$	0.195	0 621	Rat	$0.257^{412,22}$ ±0.078	0.129 ±0.046	0 525 ±0.184
Guinea pig	$0\ 583^{53,2}$	0 142	0.256	Monkey	$3\ 75^{127,23}$ ±1 09	0.891 ±0.397	0.235 ±0.065
Hamster	$0.121^{114,8}$ ±0 015	0 043 ±0.016	0.372 ±0.170	Mouse	$0.0248^{48,6}$ ±0 0049	0.0257 ±0 016	1 044 ±0 588
Sheep	$41.8^{28,3}$ –[b]	8.51 ±3.5	0.204 ±0 084	Pig	$28^{19,1}$	6 7	0.24

[a] Superscripts in the body weight column are number of animals and number of experiments involved in the mean values, respectively.
[b] Body weight value for sheep is artificial, calculated from a minute volume provided as l min^{-1} m^{-2} body surface using the formula given by the author for calculating surface area from body weight. The value for minute volume is the quoted value in l min^{-1} m^{-2} and the body weight value is the corresponding weight in kg 1 m^2

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specific controlled physiological states e.g. resting, exercise, anaesthesia and disease, which may differ significantly from the condition of the test animals. Therefore, for this study, the human values were generated from the animal data and compared to the human studies after the fact. Several papers[31–33] describing marine mammals were excluded because of the adaptation to underwater lifestyle involving periodic or infrequent breathing and extended breath-holding. Because the ultimate aim was to predict the values in young adult humans from those in other species of young adult terrestrial mammals, and because the values for newborn and very young animals were quite different from adult values,[4,34] the data from newborn and prepubescent animals also were excluded (see Tables 4 and 5).

When the data for non-anaesthetized animals of all species were plotted as $\log_{10}$ of minute volume vs. $\log_{10}$ of body weight (Figs 1 and 2), a straight line resulted (power law curve; Fig. 2) with a correlation coefficient of 0.975 (see Eqn. (3)). In Fig. 1, the species involved are identified and the range for humans is indicated.

Analysis of the variability in this full data set indicated that several studies were indeed statistically separate from the main body of the data. These included the cat studies by Wang and Nims,[23] the cotton rat data of Guyton[2] and the spiny anteater study by Bentley *et al.*[35] With these data removed, the final data set for non-anaesthetized mammals contained data from 142 studies on 18 species and 2616 animals.

Analysis of the data set. A model for the respiratory system,[36] based on a geometrically self-similar (fractal) network of flexible cylindrical tubes, suggests that the minute ventilation, V_m, and body mass, BW, are characterized by an allometric scaling relation of the form

$$V_m = kBW^{3/4} \qquad (1)$$

where k is a 'universal' constant and the power of BW, i.e. 3/4 or 0.75, is referred to as the scaling exponent or constant.[36–38] When the collected data for non-anaesthetized animals were fitted to this equation, the calculation showed an 'anomalous' scaling for the minute ventilation against body mass (weight), with a scaling exponent of 0.80 that is close to but higher than the theoretical value of 0.75.

The measured allometric scaling relationship for minute ventilation and body mass for the compiled data set is shown in Fig. 2. In particular, V_m displays a scaling range of about four decades with respect to BW, over which the observed relationship is seen to increase linearly on a double logarithmic plot. We conclude that V_m follows a power law distribution of the form

$$\log_{10}V_m = b + a\log_{10}BW \text{ or } V_m = k\,BW^a \qquad (2)$$

where $b = \log_{10}k$. A power law distribution indicates the lack of a characteristic scale. A linear regression of the data collected gives values (mean ± SD) for the constants in Eqn. (2) of: $b = -0.302 \pm 0.015$ and $a = 0.809 \pm 0.010$. This relationship explains 97.5% of the variation in the data. The least-squares fitted line is shown by the solid line in Fig. 2 and the broken lines delineate the 99% simultaneous confidence bands for the fitted line. In the form of Eqn. (2), the regression equation would be

$$\log_{10}V_m = -0.302 + 0.809\log_{10}BW$$
$$\text{or } V_m = 0.499\,BW^{0.809} \qquad r^2 = 0.975 \qquad (3)$$

where the units of minute volume V_m and body weight BW are l min^{-1} and kg, respectively.

A normal quantile plot of the residuals from the least-squares fitted line (i.e. the difference between the measured minute ventilation rates and the minute volumes predicted by Eqn. (3); Fig. 3) shows that the residual distribution appears to be approximated well by a Gaussian distribution. Nevertheless, there does appear to be a small amount of skewness in the data at the extreme upper and lower tails of the residual distribution. Here, it is seen that the points in the upper and lower tails lie somewhat below and above the line, respectively, suggesting that the residual quantiles here are slightly smaller and larger, respectively, than that expected for a Gaussian distribution. The influence of these points on the least-squares fit appears to be minimal. In particular, the use of a highly robust method for fitting a linear regression based on minimizing the sum of the q smallest squared residuals (i.e. the least-trimmed-squares regression) gave essentially the same values for parameters a and b (c.f. Eqn. (2)), namely $b = -0.286 \pm 0.008$ and $a = 0.798 \pm 0.007$. Therefore, the simple regression was considered to be sufficient.

Interestingly, the observed allometric scaling relationship between V_m and BW yields a scaling exponent of 0.80 rather than the theoretical value of 0.75. The difference between these two values of scaling exponent is admittedly small, but this difference was statistically significant. Indeed, if a fitted function of the form of Eqn. (2) with $a = 0.75$ suffers from a lack of fit to the data, then the aspect of the underlying pattern not accounted for by the fit should be evident in the residuals. Figure 4 shows the residuals $\epsilon = \log_{10}V_m - 0.75\log_{10}BW$ plotted against $\log_{10}BW$. Note that these residuals show a clear positive linear trend, implying that V_m varies with BW with a scaling exponent that is greater than the putative 0.75 provided by theory. A locally weighted regression smoother (loess curve)[39] was used to analyse the residuals. This method is attractive because it relies upon the data (e.g. the residuals in our case) to specify the form of the model. In loess smoothing, a curve (or smooth function) is fitted to the data points locally so that any point on the curve depends only on the observation at that point and some specified neighbouring points. The loess curve, added to Fig. 4, shows the residual dependence of ϵ on $\log_{10}BW$. However, a plot of the residuals $\epsilon = \log_{10}V_m - 0.80\log_{10}BW$ vs. $\log_{10}BW$ (Fig. 5) does not appear to show any systematic trends. Indeed, fairing a loess curve through these residuals shows only a constant variation with $\log_{10}BW$; in particular, the constant value indicated by the loess curve for the residual variation is about -0.29, which coincides (approximately or better) with the least-squares-fitted value for $b = -0.302 \pm 0.015$.

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Table 4. Data collected from non-anaesthetized animals

Species	Physiological state and details	Body weight *BW* (kg)	Number of animals	Minute volume *MV* (l)	$\frac{MV}{BW}$	Ref.
Monkey	Chair, 30 min	2 80	60	1.487	0.531	19
Monkey	Str jacket, 30 min	2.80	60	1.587	0.567	19
Monkey	Sedated, conscious	3.00	3	1 000	0.333	c
Monkey	Sedated	3.50	16	1.200	0.343	d
Monkey	Sedated	3.50	3	1 400	0.400	d
Monkey		2 68	6	0.863	0 322	2
Monkey, Rhesus	Chair	10 70	3	2.000	0 187	54
Monkey, Rhesus	Chair	10 90	6	2.000	0 183	55
Monkey, Rhesus	Untrained, quieted	2 63	39	1.014	0.386	56
Monkey, Rhesus	Untrained, quieted	3.49	4	0.757	0.217	56
Monkey, Rhesus	Conscious, O_2	4.05	4	1 100	0 272	20
Monkey, Rhesus	Female, chair	3.33	8	1.820	0.547	57
Monkey, Rhesus	Male, chair	3 48	8	1.441	0.414	57
Monkey, cynomolgus	Chair	4 25	10	2.039	0 480	58
Monkey, cynomolgus	Chair	3.00	81	1.272	0.424	59
Monkey, pygmy[a]	Free, infant	0.68	1	0.400	0.588	13
Baboon	Chair	4.42	4	1.612	0 365	58
Cat	Trained, free	3 00	4	0.804	0.268	16
Cat	Trained, awake, not purring	3 40	6	0.840	0 247	60
Cat	Trained, plethysmograph	2 80	11	0.950	0 339	61
Cat	Trained	3.62	6	0.830	0 229	62
Cat	Trained, plethysmograph	4 00	5	0.800	0.200	63
Cat[b]	Trained, plethysmograph	2.23	4	0.475	0 213	23
Cat[b]	Trained, plethysmograph	2.55	4	0.490	0 192	23
Cat[b]	Trained, plethysmograph	2.58	4	0 373	0.145	23
Cat[b]	Trained, plethysmograph	2 35	4	0.284	0.121	23
Cow	Standing, stanchion	439	4	78.4	0 179	64
Calf, Ayrshire[a]	8 months standing, stanchion	147	4	31.3	0 213	65
Cow, Br. Swiss	Stanchion, raised 50°F	250	3	44.0	0 176	66
Cow, Br. Swiss	Stanchion, raised 50°F	325	3	50 2	0 154	66
Cow, Brahmin	Stanchion, raised 80°F	350	3	37.9	0.108	66
Cow, Brahmin	Stanchion, raised 80°F	250	3	34 0	0.136	66
Cow, Guernsey	Stanchion	435	2	126 7	0.291	67
Cow, Guernsey	Standing	410	1	107 0	0 261	30, 68
Cow, Hereford	Standing	422	1	109.0	0.258	30, 68
Cow, Hereford	Standing	144	1	49.0	0 340	30, 68
Cow, Holstein	Standing	514	1	114 0	0.222	30, 68
Cow, Holstein	Standing	164	1	61 0	0.372	30, 68
Cow, Holstein	Stanchion, raised 50°F	250	3	51.4	0.206	69
Cow, Holstein	Stanchion, raised 50°F	350	3	66 5	0.190	69
Cow, Jersey	Stanchion	340	1	59.3	0.174	67
Cow, Jersey	Standing	403	1	92.0	0.228	30, 68
Cow, Jersey	Stanchion, raised 50°F	225	3	39.1	0 174	69
Cow, S. Gertrudis	Stanchion, raised 80°F	250	3	49.7	0 199	69
Cow, S. Gertrudis	Stanchion, raised 80°F	350	3	55 9	0.160	69
Cow, Shorthorn	Stanchion, raised 50°F	250	3	45 8	0.183	69
Cow, Shorthorn	Stanchion, raised 50°F	350	3	49.1	0 140	69
Cow, Guernsey[a]	Stanchion, raised 50°F	110	3	5 6	0.051	66
Cow, Br Swiss[a]	Stanchion, raised 50°F	100	3	23.7	0.237	66
Cow, Brahmin[a]	Stanchion, raised 80°F	100	3	19.1	0.191	60
Cow, Hereford[a]	4–6 weeks, plethysmograph	59	8	13.1	0 222	70

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Table 4. Continued

Species	Physiological state and details	Body weight *BW* (kg)	Number of animals	Minute volume *MV* (l)	$\frac{MV}{BW}$	Ref.
Cow, Holstein*	Stanchion, raised 50°F	100	3	25.5	0.255	69
Cow, Jersey*	Stanchion, raised 50°F	100	3	21.9	0.219	69
Cow, S. Gertrudis*	Stanchion, raised 80°F	100	3	27.4	0.274	69
Cow, Shorthorn*	Stanchion, raised 50°F	100	3	35.4	0.354	69
Steer, Hereford*	Stanchion,5200 ft altitude	233	10	91 0	0.391	71
Dog, Beagle		11.3		3.60	0.319	72
Dog, Beagle		11.2		3 90	0.348	72
Dog, Beagle	13 months, 5500 ft attitude Albuquerque, NM	9.2	39	5.28	0.577	73
Dog, Beagle		10 5	20	3.14	0.299	74
Dog, Beagle	1 year	9.2	140	3.60	0.391	72
Dog, Beagle	5 years	11.2	48	3 90	0.348	72
Dog, Beagle	10 years	11.3	50	3 60	0.319	72
Dog, Beagle	Restrained	9.6	49	4.47	0.465	75
Dog, Beagle	Female, 12–14 months	8.4	50	3.60	0.429	76
Dog, beagle	Female, 3–4 years	10.0	10	3.61	0.361	76
Dog, Beagle	Female, 8–10.5 years	10.9	36	3.81	0.350	76
Dog, beagle	Male, 12–14 months	10.0	50	3.65	0.365	76
Dog, beagle	Male, 3–4 years	12.0	10	4.51	0.376	76
Dog, Beagle	Trained, free	9.0	12	3.30	0 367	14
Dog, Beagle	Free	9 0	60	3 70	0 411	6
Dog	Trained	11 6	92	4.56	0.393	77
Dog	Trained	10.6	32	2.27	0.214	78
Dog	Trained, during exposure	10.6	32	2.55	0.241	78
Dog	Restrained plethysmograph	59.0	1	11.70	0 198	67
Dog	Restrained plethysmograph	13 5	1	6.60	0.489	67
Dog	Restrained, plethysmograph	15 6	5	3.41	0.219	79
Dog, Beagle*	0.25 year	3 1	10	1 80	0.581	72
Puppy*	Newborn, free	0 297	3	0 428	1.440	53
Guinea pig	Free	0 466	61	0.156	0.334	2
Guinea pig	Trained, free	0.512	10	0.171	0.334	14
Guinea pig	Trained, free	0.194	8	0.162	0.835	15
Guinea pig	Trained, free	0 212	5	0 154	0.724	15
Guinea pig	Restrained	0 345	24	0.236	0 684	[b]
Guinea pig	Restrained	0.245	26	0 157	0.641	[b]
Guinea pig	Plethysmograph, intrathoracic catheter	0.219	200	0.139	0.635	10
Guinea pig	Plethysmograph, intrathoracic catheter	0.215	85	0.139	0.644	80
Guinea pig	Plethysmograph, intrathoracic catheter	0 209	60	0.137	0 656	10
Guinea pig	Free, contained	0.285	6	0.142	0.498	81
Guinea pig	Free, H_2O aerosol	0.285	6	0.149	0.522	81
Guinea pig	Free	0.588	1	0.226	0 384	[b]
Guinea pig	Free	0 312	1	0.209	0 670	[b]
Guinea pig	Free	0.278	1	0.204	0.733	[b]
Guinea pig	Free	0 329	1	0.242	0.736	[b]
Guinea pig	Free, sedentary	0.337	8	0.183	0.542	82
Guinea pig	Free, enclosed	0.320	4	0.157	0.490	83
Guinea pig	Pleural catheter, pre-anaesthetized	0.402	10	0.244	0.607	84
Guinea pig	Pleural catheter, pre-anaesthetized	0.380	15	0.252	0 663	85

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Table 4. Continued

Species	Physiological state and details	Body weight *BW* (kg)	Number of animals	Minute volume *MV* (l)	$\frac{MV}{BW}$	Ref.
Goat	Trained, masked	52 5	3	12.3	0.235	86
Goat	Laterally recumbent, awake	23 7	21	5.7	0.242	87
Goat	Stanchion	31.5	4	10.7	0.341	67
Goat	Trained, masked	40.0	10	9.4	0 235	88
Hamster	Free	0.111	10	0.050	0 452	11
Hamster	Trained, free	0 110	10	0 050	0.455	14
Hamster	Quiet (asleep?)	0.130	12	0 042	0.323	89
Hamster	Free	0.092	65	0.061	0.665	2
Mouse	Free	0 0198	56	0.0245	1.239	2
Mouse		0.0271	5	0.0520	1.919	90
Mouse		0.0120	6	0 0200	1.667	91
Mouse*	Free	0.0105	10	0 0150	1.429	92
Mouse, C57	Free	0 0240	7	0 0273	1.138	93
Pony	Free	205	1	19.9	0 097	7
Pony	Free	135	1	23.2	0 172	7
Pony	Free	161	1	45.2	0 281	7
Horse, Morgan	Treadmill trained	476	5	65	0.137	94
Horse	Standing	422	2	60	0.142	95
Horse, thoroughbred	Standing	486	15	79	0 163	96
Horse, mixed	Standing tied	476	5	44	0 093	67
Donkey	Stanchion	120	1	19.5	0.163	67
Mule	Stanchion	210	1	30.1	0.143	67
Mule	Stanchion	210	1	21.7	0.103	67
Rabbit	Trained, free	3.00	9	1.240	0.413	14
Rabbit	Awake, restrained	3 25	10	1 503	0.463	'
Rabbit	Trained, free	2.05	42	1 615	0.787	6, 97
Rat	Free	0.400	16	0 223	0 558	6, 16
Rat	Trained, free	0.383	10	0 215	0 561	14
Rat, Fischer 344	Female, free, enclosed	0.155	8	0.070	0 452	18
Rat, Fischer 344	Free, enclosed	0.207	7	0.118	0 570	18
Rat, white	Free	0 310	1	0.066	0.213	95
Rat	Head electrodes	0 300	5	0.141	0.470	98
Rat	Quiet, awake	0.300	5	0.153	0.510	99
Rat	Porton	0 198	5	0.199	1 008	100
Rat	18 weeks, free	0 299	10	0.225	0.753	101
Rat	10 weeks, free	0 211	10	0.161	0.761	101
Rat	3–6 months, Plethysmograph, whole body	0 303	36	0.273	0.899	102
Rat	3–6 months, Plethysmograph, whole body	0.303	67	0.236	0.780	102
Rat	Trained, free	0.250	16	0.140	0.560	59
Rat	Trained, free	0.250	12	0.155	0.625	59
Rat		0.284	8	0.276	0.971	103
Rat	Unrestrained	0.305	8	0.214	0 701	103
Rat		0.250	4	0.238	0 950	12
Rat	Free	0.198	5	0.199	1.008	100
Rat	Free	0.238	14	0 388	1 630	12, 104
Rat	Free	0 229	14	0.336	1 467	12, 105
Rat	Free	0 111	23	0.228	2 054	12, 105
Rat, white*	Free	0 113	35	0.073	0.646	2

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Table 4. Continued

Species	Physiological state and details	Body weight *BW* (kg)	Number of animals	Minute volume *MV* (l)	$\frac{MV}{BW}$	Ref.
Rat[a]	5 weeks, Free	0 052	10	0.087	1.662	101
Rat[a]	7 weeks, Free	0 110	10	0.113	1.028	101
Cotton rat[b]	Free	0 077	27	0.040	0.516	2
Sheep	Stanchion	52.0	1	28 0	0.539	67
Sheep	Thermoneutral water bath	59 9	4	7.10	0.119	30, 106
Sheep	Air	77 0	1	10.2	0.133	107
Sheep	Air	71 0	1	9.4	0.133	107
Sheep	Thermoneutral water bath	70.0	1	11.4	0.163	107
Sheep	20°C environment	52.0	1	28.0	0.538	67
Sheep	Temperature study	29.0	2	13.8	0 477	108
Sheep[j]	Light, thiopentone	41.8	13	12 53	0 300	109
Sheep[j]	Light, thiopentone	41.8	9	11 34	0 271	109
Sheep[j]	Light, thiopentone	41.8	2	9 91	0 237	109
Sheep[j]	Light, thiopentone	41.8	11	11 39	0.272	109
Pig, female	6 months, restrained	170	1	19	0 112	67
Pig, female		225	1	37	0.164	30, 110
Piglet	Free, contained	1.63	11	1 185	0.727	111
Giraffe	Free standing	544	2	74 3	0.136	64
Spiny anteater[b]	Female, quiet, restrained, asleep?	3.35	2	0 350	0.136	35
Spiny anteater[b]	Male, quiet, restrained, asleep?	3 60	1	0 704	0.196	35
Marine mammals[k]						
Harbour seal	Cheyne-Stokes respiration	27.5		3.97	0.144	31
Porpoise	In captivity	170		9.7	0 057	32
Killer whale	Beached, free	1090	1	47 8	0.044	33

[a] Excluded as too young.
[b] Excluded as outlier (see text)
[c] C. P. Dirnhuber, D. M. Green and J A Stratton, personal communication 1978.
[d] J. A G. Edginton, T J. Grace, P. N Price and D. W Swanston, personal communication, 1989
[e] Added in press, not used in calculations.
[f] T. J. Grace and M. J. Hobbs, personal communication, 1996.
[g] A C Allenby, D. W. Anderson, S C Bailey, R M. Black, J. W Scawin and D G. Upshall, personal communication, 1997.
[h] J. A G Edginton, T C Marrs, P. N Price and D G Upshall, personal communication 1984.
[i] M L M. Pitt, personal communication, 1997.
[j] Body weight value of sheep is a minute volume provided as l min^{-1} m^{-2} body surface and the body weight value is the corresponding weight in kg for 1 m^2
[k] Excluded for physiological reasons (see text)

An analysis was done with the data for anaesthetized animals with a similar result. The regression equations for the anaesthetized animals were

$$\log_{10} V_m = -0.488 + 0.789 \log_{10} BW$$

$$\text{or } V_m = 0.325\ BW^{0.789} \qquad r^2 = 0.927 \qquad (4)$$

where the units of minute volume V_m and body weight BW are l min^{-1} and kg, respectively.

There was concern that the contribution from small laboratory animals, which are physically and physiologically removed from man, would be overemphasized because of the numbers of studies and animals involved. If there was such an effect, recalculating the data using values weighted with the animal numbers should change the result in one direction, and recalculating the data using the mean values for each species should have the opposite effect. When these two extra calculations were performed, the resulting allometric equations were not significantly different and there was no apparent trend in the results. In fact, the effects noted on the non-anaesthetized and anaesthetized data sets appeared to be random. No further consideration was given to this topic.

The minute volume for a 70 kg man was calculated from Eqn. (3) (non-anaesthetized animals) to be 15.5 l min^{-1}. From Eqn. (4) (anaesthetized animals), the corresponding human minute volume was calculated to be 9.3 l min^{-1}. The 15.5 l min^{-1} value for a normally breathing, non-anaesthetized human is within the bounds of accepted values for men doing 'mild

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Table 5. Data collected from anaesthetized animals

Species	Physiological state and details	Body weight *BW* (kg)	Number of animals	Minute volume *MV* (l)	$\frac{MV}{BW}$	Ref.
Cat	Pentobarbital Na	3.70	4	0.960	0 259	1
Cat	Pentobarbital Na	3.25	6	0.785	0 242	112
Cat	Pentobarbital Na	2 80	6	0.410	0 146	113
Cat	Pentobarbital Na	2 80	11	0.550	0.196	61
Cat	Pentobarbital Na	3.20	9	1.076	0 336	114
Cat	Pentobarbital Na	3 40	6	0.840	0.247	60
Cat	Pentobarbital Na	3 40	6	0 900	0.265	60
Cat	Pentobarbital Na	2 7	5	0.5	0.19	63
Cat	Pentobarbital Na	2 5	6	0 468	0.187	115
Cat	Ketamine	3 10	10	0 489	0.158	116
Cat	Diazepam	3 40	6	1 130	0.332	60
Cat	Nembutal	2 55	4	0.250	0.098	23
Cat	Chloralose	2 60	4	0.180	0.069	23
Cat	Urethane	2 35	4	0.248	0.105	23
Cat	Alpha chloralose	2.50	19	0.381	0.152	117
Cat	Pentobarbital	3.25	7	0.355	0 109	118
Dog	Nembutal	13.5	39	6 22	0.462	119
Dog	Nembutal	10.0	8	4 00	0.400	120
Dog	Pentobarbital	12.6	4	3 10	0.246	1
Dog	Chloralose/ethyl carbamate	9 3	2	1.07	0.115	35
Dog	Female, Pentobarbital	16 8	35	1.81	0 108	121
Dog	Male, Pentobarbital	21 0	42	2.92	0.139	121
Dog, Beagle	Pentobarbital+vetame	9.0	1	1.68	0.186	22
Dog, Beagle	Pentobarbital+vetame	9.0	1	1.76	0.195	22
Dog, Beagle	Pentobarbital+vetame	9.0	1	1.82	0.202	22
Dog, Beagle	Pentobarbital+vetame	9.0	1	2.16	0.239	22
Dog, Beagle	Pentobarbital+vetame	9 0	1	2.48	0 276	22
Dog, mongrel[a]	Pentobarbital	16.3	15	6.7	0.416	122
Pig	Nembutal	28	19	6 7	0.239	119
Sheep	Na thiopentone	41.8[b]	5	6.35	0 152	123
Sheep	Na thiopentone	41 8[b]	7	6.67	0 159	124
Sheep	Na thiopentone	41 8[b]	13	12 53	0.300	124
Ferret	Pentobarbital	0 314	18	0.195	0 621	5
Guinea pig	Pentobarbital Na	0 690	4	0 130	0.188	1
Guinea pig	Ether	0 477	49	0 154	0.323	2
Hamster	Male, pentobarbital Na	0 132	27	0.045	0.341	125
Hamster	Female, pentobarbital Na	0.136	27	0 040	0.294	125
Hamster	Ether	0 096	34	0 048	0 499	125
Hamster	Chloralose/ethyl carbamate	0.110	7	0 072	0.650	35
Hamster	15 weeks, halothane	0.126	10	0 028	0.221	126
Hamster	65 weeks, halothane	0.125	9	0 028	0.225	126
Giraffe	Free standing	544	1	61	0 111	64
Mouse	Pentobarbital Na	0.0320	4	0 0210	0.656	1
Mouse	Pentobarbital	0.0271	5	0.0207	0.764	90
Mouse	Chloralose/ethyl carbamate	0.0270	10	0.0560	2.074	35
Mouse	Ether	0 0188	7	0.0177	0.941	2
Mouse	Ether	0 0207	15	0.0281	1 357	2
Mouse, C57	Pentobarbital Na	0 0230	5	0.0108	0 470	93
Rabbit	Pentobarbital Na	2.400	4	0.620	0.258	1
Rabbit	Chloralose/ethyl carbamate	1.800	4	0 450	0.250	35
Rabbit	Ether	2.069	31	0 800	0.387	2
Rabbit	0 5–1 year, pentobarbital Na	4 100	15	0.773	0 188	127
Rabbit	3–5 years, pentobarbital Na	4.100	20	0.694	0 169	127
Rat	Chloralose/ethyl carbamate	0 215	16	0.152	0 707	35
Rat	Urethane	0 163	21	0.119	0.732	12
Rat	Urethane	0.230	18	0 146	0.635	12
Rat	Urethane	0 285	24	0.171	0.600	12
Rat	Urethane	0.323	14	0.127	0.393	128, 129
Rat	Urethane+allobarbital	0.195	10	0.092	0.472	12, 128, 129
Rat	Halothane	0.200	20	0.054	0.270	130
Rat	Urethane	0.206	67	0.085	0.416	12, 131
Rat	Halothane, light	0 229	10	0.203	0.886	12
Rat	Halothane, light	0.220	10	0.132	0.600	12
Rat	Halothane, light	0.234	9	0.149	0.637	12
Rat	Halothane, light	0.266	8	0.189	0.711	12
Rat	Halothane, light	0.280	7	0.115	0 411	12
Rat	Pentobarbital Na	0.250	4	0 160	0 640	1
Rat, B&W hooded	Female, pentobarbital Na	0.257	28	0.111	0.432	125
Rat, B&W hooded	Male, pentobarbital Na	0.464	30	0 207	0 446	125

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Table 5. Continued

Species	Physiological state and details	Body weight *BW* (kg)	Number of animals	Minute volume *MV* (l)	$\frac{MV}{BW}$	Ref.
Rat, Fisher	Urethane	0.233	32	0.161	0 691	132
Rat, white	Ether	0.110	32	0.076	0 688	2
Rat, white	Thiamyl	0 402	12	0.175	0 435	133
Rat	102 days, Halothane	0 222	20	0 054	0 243	134
Rat	538 days, Halothane	0 334	10	0 082	0 246	134
Rat	815 days, Halothane	0 332	10	0 082	0.247	134
Monkey	Semyl	2.80	2	0.530	0 189	19
Monkey	Pentobarbital Na	2 45	4	0 700	0 286	1
Monkey	Ketamine	2 61	1	0 480	0.184	c
Monkey	Ketamine	3.03	1	0 600	0.198	c
Monkey	Ketamine	3 53	1	0.900	0.255	c
Monkey	Ketamine	3.33	1	0.900	0.270	c
Monkey	Ketamine	3.32	1	0.800	0.241	c
Monkey	Ketamine	2.71	1	0.750	0 277	c
Monkey	Ketamine	3.66	1	1.100	0.301	c
Monkey	Ketamine	3 31	1	1.000	0.302	c
Monkey	Ketamine	3.50	1	0.900	0.257	d
Monkey	Ketamine	3.50	1	1.000	0 286	d
Monkey	Pentobarbital	3.50	1	0 546	0.156	94
Monkey, Rhesus	Pentobarbital	7 56	6	1 710	0.226	135, 136
Monkey, Rhesus	Tileamine	3 30	10	0 462	0.140	21
Monkey, Rhesus	Ketamine+acepromazine	3 30	10	0.442	0 134	21
Monkey, Rhesus	Ketamine	3 30	10	0.575	0 174	21
Monkey, Rhesus	Pentobarbital	4 25	11	1.650	0 388	136, 137
Monkey, Rhesus	Pentobarbital	7 60	6	3 860	0 508	136
Monkey, Rhesus	Pentobarbital	3.49	4	0.681	0.195	57
Monkey, Rhesus	Pentobarbital	4.30	21	0 709	0 165	138
Monkey, Rhesus	Phencyclidene	5.80	14	1 791	0.309	136, 139
Monkey, Rhesus	Pentobarbital, O_2	5.05	9	0.900	0 178	20
Monkey, Rhesus	Pentobarbital	5 05	9	1.360	0.269	20
Monkey, pig-tailed		4.48	10	1.350	0.300	140
Monkey, pig-tailed		4.47	11	1.390	0 310	141

[a] Added in press, not used in calculations.
[b] Body weight value for sheep is artificial, calculated from a minute volume provided as l min^{-1} m^{-2} body surface using the formula given by the author for calculating surface area from body weight. The value for minute volume is the quoted value in l min^{-1} m^{-2} and the body weight is the corresponding weight in kg for 1 m^2
[c] J. A G Edginton, T. J. Grace, P. N. Price, P. Rice and D G. Upshall, personal communication, 1990.
[d] J. A G Edginton, T. J. Grace, P. N. Price and D. W. Swanston, personal communication, 1989

activity'[28,40–43] and slightly lower than values measured in soldiers carrying light loads while walking on treadmills.[29] It should be noted that this is not a 'resting' value for humans but rather a value corresponding to mild activity under non-stressed conditions. In turn, this value indicates that the animals were not in a 'resting' state either.

Evaluation of the data from previous studies

Seven allometric studies providing comparisons of minute volume/body weight respiratory values were found in published papers.[1–8]

The study by Stahl,[8] unfortunately does not provide a detailed database so the published equations could not be verified. However, the references indicate that the data are included in the present study. The allometric equation relating body mass and minute volume was

$$V_m = 0.379\ BW^{0.80} \qquad (5)$$

where V_m is in l min^{-1} and BW is in kg.

There are three data sets quoted in a text by Phalen[24] and the pioneering work of Guyton[2] is described without presenting the data. The first data set, taken from Crosfill and Widdicomb[1] (Table 1), describes anaesthetized animals with much lower breathing rates. The second data set was adapted from a paper by Boyd and Mangos[3] which, in turn, was compiled from other papers using both non-anaesthetized and anaesthetized animals. The third set was adapted from a paper by Mauderly[7] describing data from non-anaesthetized animals. All of the original papers from these three studies have been obtained and the data are included in the data tables presented in this study. Comparison of the data in the three data sets indicates the wide range of values for respiratory parameters that may be found in the literature. As the data were appropriately included in the data tables of this review, no further work was done with the data sets of Boyd and Mangos[3] and Mauderly.[7]

An allometric relationship was calculated for the data of Crosfill and Widdicomb[1] to be

$$\log_{10} V_m = -0.485 + 0.810 \log_{10} BW$$
$$\text{or } V_m = 0.327\ BW^{0.810} \qquad r^2 = 0.960 \qquad (6)$$

From this relationship, the human respiratory minute volume was calculated to be 10.2 l min^{-1} for a 70 kg man.

The data used by Guyton[2] (Table 1) were split into anaesthetized and non-anaesthetized groups, and

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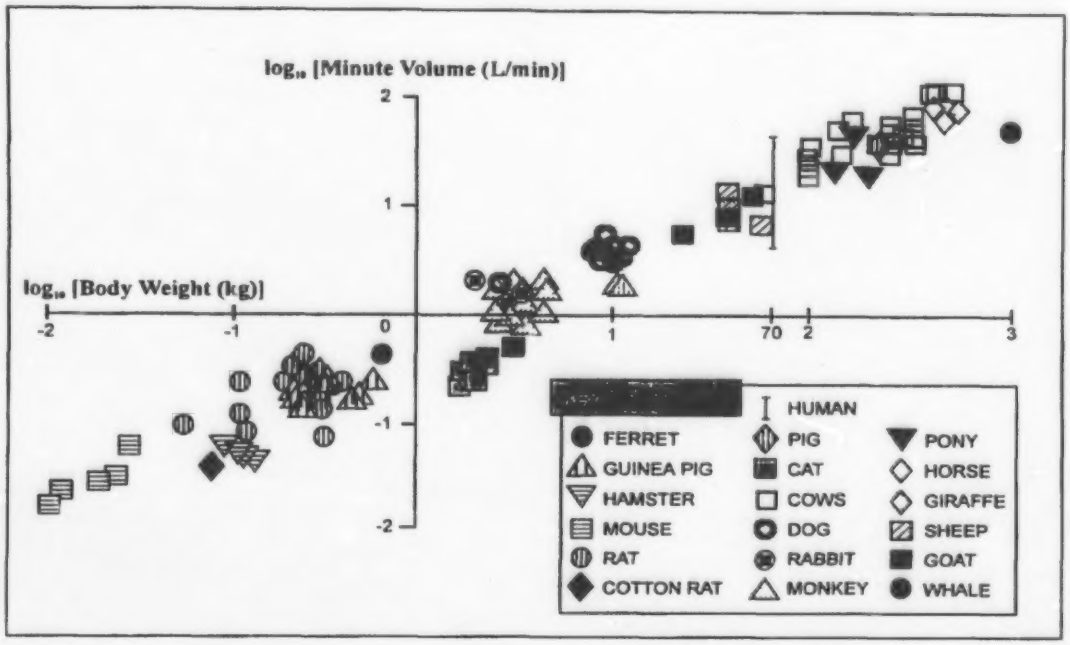

Figure 1. Body weight and minute volume of representative animal data in the collected database. The data show an allometric relationship on this log–log plot that is linear. The data represent the range from a mouse (0.012 kg) to a whale (1090 kg). A vertical line denotes the expected human values for minute volume from 6 to 30 l min^{-1} for a 70 kg man.

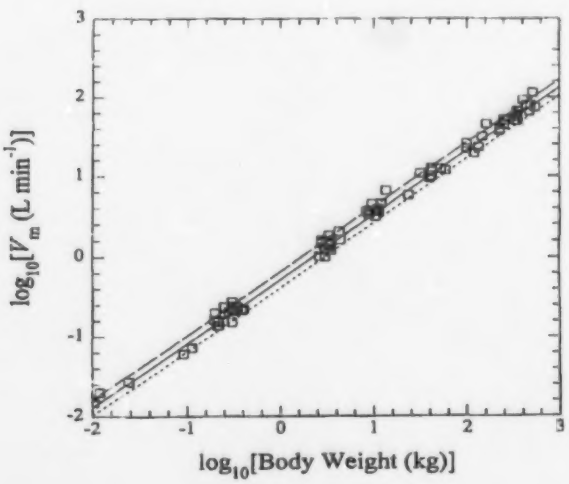

Figure 2. A statistical plot of the allometric equation for non-anaesthetized animals (solid line) and the statistical error limits (broken lines). For this plot, the final data set was used. Marine mammals, very young animals and several groups of outlying data have been excluded. The fit of the regression line is very good (r^2 = 0.975).

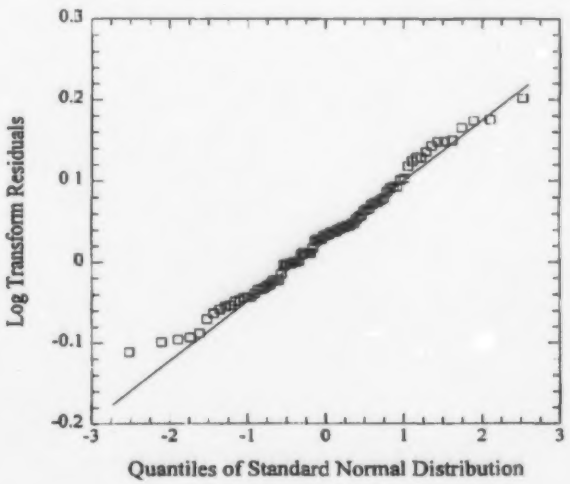

Figure 3. A quantile plot of the residuals from the fitted line describing the difference between the measured and the predicted logarithmic minute ventilation rates.

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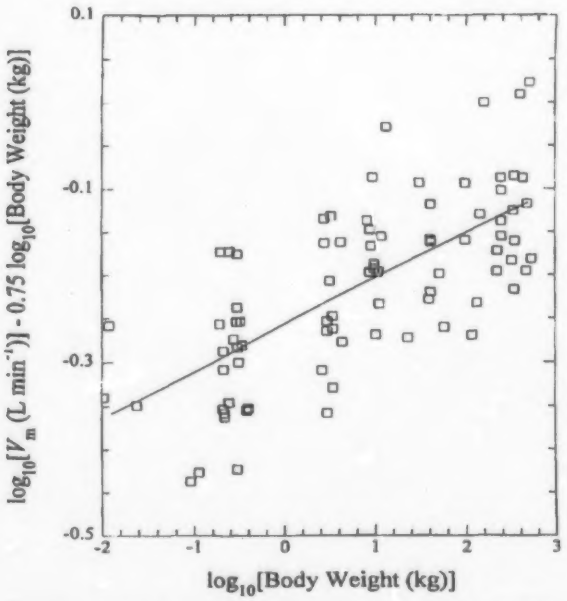

Figure 4. When the power law exponent is assumed to be 3/4, the plot of residuals vs. body weight indicates an upward trend (solid line) This suggests that V_m varies with BW with a greater than 0 75 scaling component.

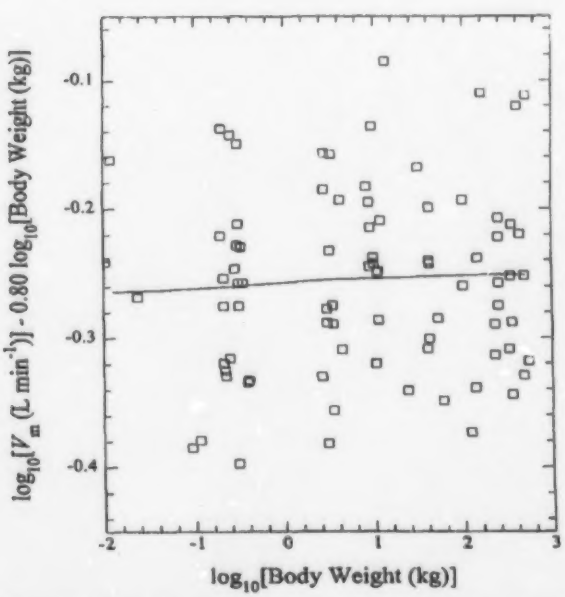

Figure 5. When the power law exponent is 0.80, the plot of residuals vs. body weight does not show any systematic trends (solid line), suggesting that all of the variability in the data is accounted for in the allometric equation

regression lines in the form of Eqn. (2) were calculated for each.

Anaesthetized:

$$\log_{10}V_m = -0.386 + 0.750 \log_{10}BW$$
$$\text{or } V_m = 0.411\ BW^{0.750} \quad (7)$$

Non-anaesthetized:

$$\log_{10}V_m = -0.458 + 0.763 \log_{10}BW$$
$$\text{or } V_m = 0.348\ BW^{0.763} \quad (8)$$

Guyton's published equation, in which the units were $cm^3\ min^{-1}$ for V_m and grams for BW, becomes

$$\log_{10}V_m = -0.412 + 0.750 \log_{10}BW$$
$$\text{or } V_m = 0.388\ BW^{0.750} \quad (9)$$

when adjusted to the units used in this study. From Eqs (7) and (8), it is obvious that the regression lines of the log–log format are similar: slightly separated but not parallel (the slope values a are only slightly different and the intercept values b are close but not equal). The original combined Guyton data set produces a regression line (Eqn. (9)) that falls between those for the anaesthetized and non-anaesthetized animals. For a 70 kg human, Eqs (7)–(9) may be evaluated to give minute volume values of 10.0, 8.9 and 9.4 l min $^{-1}$, respectively, for humans in similar physiological states to the respective animal populations. It will be noted that the predicted human minute volumes are inverted, i.e. anaesthetized > non-anaesthetized.

The data quoted by Snipes[3] were treated in a similar manner to obtain

$$\log_{10}V_m = -0.273 + 0.741 \log_{10}BW$$
$$\text{or } V_m = 0.533\ BW^{0.741} \quad (10)$$

where the minute volume V_m is in l min^{-1} and body weight BW is in kg. A value of 12.4 l min^{-1} was obtained from these equations for a 70 kg man in similar physiological condition. This value is not the value of 20 l min $^{-1}$ given by Snipes adapted from Schlesinger[43] and Snyder *et al.*[28] for a 70 kg man doing 'light activity'.

The United States Environmental Protection Agency (USEPA) published recommended values[4,34] for animal growth, feeding and respiration '... to be used only when the study under review does not report values for the biological variables required for the risk assessment ...'. The database has 87 papers yielding 203 entries encompassing 2570 animals of 44 species. Of these, eight human studies contribute 22 entries and 301 'animals'. Six papers concern wildlife of 17 species. Nine species are birds and reptiles. In 17 entries, the numbers of animals are not reported. In the remainder, the common laboratory species predominate and a number of studies include very young animals. Some of the studies are more recent than the majority of those reviewed here and, in the case of laboratory animals, more detailed because the different strains of the laboratory species are identified separately. Twenty-two of the 87 references are common to this review and

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the USEPA document. Unfortunately, those common references include both anaesthetized and non-anaesthetized animals. A number of the titles of the other references indicate that anaesthetics may have been employed. The USEPA documents[4,34] also give allometric equations for many of the species represented in their database. However, the correlation coefficients are poor in comparison to that of the total database, and calculations of the minute volumes for the 'standard' body weights produce some values that are considerably different from the experimental data. The use of the allometric equations for the separate species would appear to result in greater errors than would result from application of the total database equations.

The summary tables in the USEPA document list the units of body weight as kg and of respiratory volume as m^3 day^{-1}. The quoted equation for the relationship between daily respiration (minute volume) and body weight is

$$I = 0.66\ BW^{0.7579} \tag{11}$$

where I is the daily respiration (m^3 day^{-1}) and BW is the body weight (kg). This equation becomes

$$\log_{10} V_m = -0.339 + 0.758 \log_{10} BW$$
$$\text{or } V_m = 0.458\ BW^{0.758} \qquad r^2 = 0.96 \tag{12}$$

when the units of minute volume (V_m) are l min^{-1} and the body weights (BW) are in kg. We were unable to reproduce this regression from the published database (data excluded by the USEPA were either included or excluded). Several attempts were made, without success, to reproduce the USEPA equation with modified data, including removing the human data, weighting the data by the animal numbers and working with the average values for each species. The following equations were calculated from the USEPA data set

$$\log_{10} V_m = -0.384 + 0.763 \log_{10} BW$$
$$V_m = 0.413\ BW^{0.763} \qquad r^2 = 0.960 \tag{13}$$

using minute volume (V_m) in l min^{-1} and body weight (BW) in kg. The minute volume values for a 70 kg human calculated from Eqs (12) and (13) were 11.5 and 10.6 l min^{-1}, respectively. In a separate document,[34] the USEPA states that the default body weight for the human is defined to be 70 kg, and the V_m is defined to be (13.8 l min^{-1}) 20 m^3 day^{-1}.

DISCUSSION

The object of the exercise was to compile the data needed to obtain an estimate of the inhalation toxicity to young adult humans (specifically soldiers in this case) from inhalation toxicity values determined for a variety of animal species. To achieve this, a relationship must be established between the respiratory physiology of the animal and human subjects.

The database gathered and analysed is not complete and it is recognized that more information is available. However, the database is sufficiently large that the addition of more animals and studies will not alter the calculated values significantly. Since the preliminary reports of this study[44,45] eight studies with 312 animals have been added to the database. The slope constant a for the equation for non-anaesthetized (normal) animals was altered from 0.802 ± 0.011 to 0.809 ± 0.010 and the intercept constant b from −0.286 ± 0.017 to −0.302 ± 0.015. In the equation for anaesthetized animals, the slope constant changed from 0.782 to 0.789 and the intercept from −0.509 to −0.488. The calculated minute volume for a 70 kg man slipped from 15.64 to 15.52 l min^{-1}. None of these shifts were statistically or biologically significant. In this study, extra significant digits are reported in several places in an attempt to indicate the effects of number round-off. All statistical calculations were carried out with 14 decimal places to minimize the effects of computer concatenation of squared numbers, which ranged from the squares of 0.012 kg (body weight of mouse) to 550 kg (body weight of giraffe).

Many of the data represent relatively old studies. Newer work may be available but, in many cases, the development of respiratory science has resulted in the reporting of more complex respiratory parameters to the exclusion of the simpler respiration rates and tidal/minute volumes required for the type of analysis presented here.

Three of the studies relating body weight and respiratory function that have been used and documented in the past are described above.[2–4] The earliest and most quoted is that of Guyton,[2] who used a mixture of anaesthetized and non-anaesthetized animals. When these are separated, the data become scant. Although in the body weight/minute volume relationships (correlation regression lines) the slopes are only slightly different (0.750 vs. 0.763), the intercept values are different and the predicted minute volumes for a 70 kg man differ by ca. 10% and are reversed, i.e. the predicted minute volume of the anaesthetized humans was greater than that of the non-anaesthetized humans. In the data reported by Snipes,[3] there are fewer species, no large species and the data could not be confirmed readily in published studies or reports. The minute volume for man calculated from the data was not the same as that quoted with the animal data. However, the average data (Table 1) are quite similar to those generated for the present study. The third data set, from the USEPA,[4] also contains a mixture of non-anaesthetized and anaesthetized animals, a number of studies with newborn and prepubescent animals and, upon close examination, relatively few studies but generally more recent. Comparisons of the regression equations (allometric equations) within species with those between species in the USEPA report clearly indicates that something is distorting the calculated results. A second publication[34] which quotes the first[4] for data, lists slope values within species varying between 0.512 (guinea pig) and 1.050 (rat).

We were unable to reproduce the allometric regression equations quoted in the USEPA report.[4] There are a number of plausible reasons for this. From the USEPA reports,[4,34] it is neither clear what statistical approach nor what computational assistance (computer) were used to calculate their results and, further, nothing is said about mechanisms for handling incomplete data.

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There are many entries in the USEPA set that had missing animal numbers. Data from birds and seals are included in the tables and apparently were included in the calculations, although data from reptiles were stated to have been disregarded. The discrepancies between our calculations and those reported by the USEPA are considered to be too large for round-off errors. Because the USEPA reports do not give details concerning how the calculations were done in 1988, there is the possibility of computer concatenation of squared numbers in the statistical calculations if insufficient precision was used. Finally, because we have not been able to obtain all of the original documents referenced in the USEPA study, there is also the possibility of typographical errors.

Theoretical considerations from allometric scaling models[36 38] indicate that the scaling exponent in the equations should be three-quarter power, in this case $BW^{0.75}$. The slope values calculated in this study are slightly above 0.80 or 4/5 and the statistics clearly show a significant difference between the 0.75 and 0.80 values ($P<0.01$). The literature studies generally indicate a slope value higher than the 0.75 value. The scaling factors predicted from the data of Guyton,[2] for both anaesthetized (0.75) and non-anaesthetized (0.763) groups, are similar to the predicted theoretical value of 0.75, albeit that relatively few data were involved and one study of the cotton rat was found to be an outlier in this study. The slope of the published equation in the USEPA study[4] (Eqn. (12)) was 0.758. However, the same data when recalculated (Eqn. (13)) gave a higher value (0.763). The slope calculated from the data of Crosfill and Widdicomb[1] (Eqn. (6)) was 0.810. The 0.80 value was obtained by Stahl[8] from a smaller data set. The study by Stahl[8] has been used as a reference by others:[26,46–49] '... small deviations from quarter-power scaling sometimes occur[8,27].' and 'Further progress (*in allometry*) was hampered, however, by an insistence on the 'even' somatic exponents $\frac{1}{3}$, $\frac{2}{3}$, $\frac{3}{4}$ and 1, due to what now can be seen as naive application of dimensional analysis' (italics added for clarity). The empirical nature of these calculations was also stressed in a very detailed study[27] of birds in which allometric values were not the expected simple fractions. The results of this study also clearly indicate that no artificial attempt should be made to force the body weight/minute volume relationship to fit the three-quarter-power theoretical value.

The inter-species relationship between minute volume and body weight calculated from the data assembled for this review is considered by the authors to be the best currently available for use with young adult humans. First and foremost, the calculated relationships fit, very closely, the experimental data available. The data used for the allometric calculations are all from non-anaesthetized mammals. Also, the data were deliberately selected to be from young adult mammals in order to match the target human population. Although there is a preponderance of data from smaller laboratory species, the species range from very small to very large animals (mouse to giraffe), with a reasonable number in the sizes close to man. Finally, the number of studies, species and animals included in the calculations are large enough that the addition of more data should result in small refinements only, rather than major alterations in the resulting body weight/minute volume relationship. Similar equations for anaesthetized animals are presented so that they would be available for use with toxicological studies in which anaesthetics are required by law.

There remains a moot point: would a calculation, weighted by animal numbers, provide an improved or better estimate of the relationship between body weight and minute volume? Statisticians may argue that the weighted values should be used. However, this adds importance, perhaps undue importance, to the data for small laboratory species because there are both more studies and more animals used per study. Biologically, therefore, an argument can be made to refrain from weighting the studies in an attempt to reduce the imbalance caused by large numbers of small laboratory animals. In the current study, the unweighted data from non-anaesthetized animals were used to obtain the corresponding theoretical human minute volumes. Calculations with weighted or average values did not produce significantly different results.

The minute volume and respiration rate of resting healthy men aged 20–40 years apparently do not change with age.[50–52] This may not hold for older men, as the referred values are not conclusive: one study says no change[50] and the other two indicate changes[51,52] with increasing age. As noted above, very young/newborn animals have different (higher) minute volume/body weight ratios from the adult: 0.835 vs. 0.334 for the guinea pig,[14,53] 0.54 vs. 0.27 for the cat,[16,53] 0.814 vs. 0.36 for dogs[15,53] and 0.57 vs. 0.104–0.125 for (resting) humans.[4] In general, physically fit, young adult men and women have similar minute volume/body weight ratios.[28] Another study[52] stated that there was less change in the respiratory volumes with age in the female test population than in the male test population. As the studies with animals do not give the gender in many cases, the variation due to gender was not treated in this study. However, young adult woman may be lighter than their male counterparts. Therefore, for specific studies with women, it may be in order to use a different body weight to calculate the appropriate minute volume value from the allometric relationship. In the same vein, there may be instances in which the 70 kg man does not represent the target population and a different calculation of minute volume would be used. It must be noted that, in all cases, it is assumed that the target is a fit, young adult population of humans.

When toxicity, body weight and minute volume data are available, the data may be used directly to extrapolate the toxicity to a human estimate. However, in many cases the required respiratory and body weight measurements are not available for the subjects of toxicity studies and 'standard' animal values must be applied. Examination of the data shown in Fig. 1 indicates that the minute volume and body weight in adults vary in a similar manner both within and between species. The USEPA study provides allometric equations for many of the species commonly used in toxicological studies,[4] albeit that the correlations reported for intra-species variation are not as good (possibly because of the effect of very young animals on the calculated relationships). From the mean and

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Table 6. Calculated values for the 'Standard' laboratory animals

Species	Body weight *BW* (kg)	Minute volume *MV* (l min^{-1})	$\frac{MV}{BW}$ ratio
Mouse	0.025	0.0269	1.0760
Rat	0.250	0.170	0.681
Guinea pig	0.50	0.297	0.594
Rabbit	3.0	1.249	0.416
Dog	10.	3.281	0 328
Ferret	1.1	0.559	0 508
Monkey	4 5	1.729	0 384

standard deviation values generated in this study (Table 6), it is clear that the use of data for a 'standard' animal will not create a large error if the test and 'standard' animals are not too disparate. Indeed, the use of 'standard' animal values allows[4] '... assessments made by different individuals or groups at different times ...' (*to be*) '... compared more clearly, allowing disagreements to focus on important scientific judgements rather than more mundane and trivial differences in assumptions of body weight and other biological variables.' 'Standard' animal values, given in Table 6, were calculated using the recommended allometric relationship (Eqn. (3)). The agreement with the collected data means was generally good. The mouse showed the poorest agreement for the common laboratory species.

A great deal of discussion has centred upon the respiratory values to be used for man. Because humans can communicate, it is possible to measure, accurately and readily, the respiratory values under a wide variety of physiological conditions. To obtain similar control of the values obtained with animals would require extensive effort in training the animals to both the handling and to the measurement equipment or, alternatively, the use of anaesthetics or other drugs to reduce the handling stimuli. In the early studies, anaesthetics were used. Later, measurements were made upon contained but unrestrained laboratory animals and well-conditioned larger species. Nevertheless, the exact state of excitement or agitation is generally undefined for the animals described in the accompanying data tables.

Because the physiological state of the animals is somewhat undefined and in a comparison should be as close as possible, it is not possible to define an equivalent human state. Therefore, the authors consider the best approach to be to select an appropriate body weight for the human and calculate the corresponding minute volume from the allometric relationship presented, e.g. 15.5 l min^{-1} for a 70 kg human. The assumption of a 'resting' condition for the human results in values that are somewhat removed from the predicted line, as does the assumption of 20 l min^{-1}.[3,4] In the other studies quoted, there is no general agreement on the minute volume value used for humans. Guyton[2] used a value of 6 l min^{-1} for 'resting' man that is lower than the 9.4 l min^{-1} value calculated from the data presented. Snipes,[3] quoting Snyder,[28] recommended a value of 20 l min^{-1} for man doing light activity but the data provided for the animals calculate to a value of 12.4 l min^{-1} for man. The USEPA[4] lists a combined value, also based upon Snyder,[28] which provides a daily value for a man resting for 8 h and doing mild activity for 16 h. The allometric equation calculated from the USEPA data provides a human minute volume of 10.6 l min^{-1}, which also differs significantly from the quoted reference value of 20 l min^{-1}. In a separate publication,[34] the USEPA recommends a 'default' value of 13.8 l min^{-1} for humans The International Commission on Radiological Protection (ICRP) reference man[28] breathes 23 m^3 day^{-1} (15.9 l min^{-1}) during light activity, which is close to the calculated value of 15.5 l min^{-1} obtained in this study.

The allometric equations presented provide the relationship between body weight and minute volume for a fixed set of physiological parameters. These equations cannot be used to calculate the toxicity for different breathing rates, only for a 70 kg man breathing 30 l min^{-1}. The toxicity resulting from inhaling either an air-dissolved chemical or an aerosol should be directly related to and vary with the volume of contaminated air inhaled, which may be represented by the minute volume. Therefore, the calculation of toxicity values for breathing rates other than that indicated from the allometric relationship should be a simple inverse proportion (as the toxicity increases, the LCt_{50} or LD_{50} decreases). For example, the LCt_{50} value for a 70 kg human breathing 30 l min^{-1} would be 15.5/30 or 0.52 times the LCt_{50} value for a human breathing 15.5 l min^{-1}.

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